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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,574	01/16/2001	Jean-Christophe Francis Audonnet	454313.3154.1	2896

7590 09/12/2002

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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	12

DATE MAILED: 09/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/760,574	Applicant(s) AUDONNET ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83* is/are pending in the application.

4a) Of the above claim(s) *13-17,22-43,56-59 and 64-83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,18-21,44-55 and 60-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 & 9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This action is in response to the communication filed by the applicant on July 29, 1992. Claims 1-83 are pending in the application.

Election/Restrictions

2. Applicant's election with traverse of the species BRSV in Paper No. 11, filed July 29, 2002 is acknowledged. The traversal is on the ground(s) that there is no burden to searching the additional species because 1) the number of additional species are not too great in number and 2) the requirement would create an undue burden on the Applicant because, if followed the election of species requirement would require the Applicants to file a number of additional applications. This is not found persuasive because: 1) there is burden to search the additional species because searching each of species, including the different bovine pathogens, would require searching for different elements such as the gB and gC elements of BHV-1 and the EO and E2 elements of BVDV. Furthermore it appears that Applicant is arguing that the species are not patentably distinct. However, no evidence has been presented indicating that the species are obvious variants nor is there a clear admission on the record that this is the case. 2) The examiner respectfully points out that upon the allowance of the generic claims, applicants will be entitled to consideration of claims drawn to the additional species which are written in dependent form or otherwise include all of the limitations of an allowed generic claim as provided by 37 CRF 1.141. Therefore, applicants are not required to file additional applications due to the species election requirement.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 13-17, 22-43. 56-59 and 64-83 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11, filed July 29, 2002. Claims 1-12, 18-21, 44-55 and 60-63 are examined herein.

Drawings

4. The drawings are acceptable for examination purposes.

Specification

5. The disclosure is objected to because of the following informalities: the top margin of all pages of the specification (specifically pages 71-82) does not comply with 37 CRF 1.52(a). Therefore, when holes were inserted into the specification (in order to place the specification into the file) words were cut out. Applicant must provide a substitute specification that complies with 37 CRF 1.52 paragraph (a)(1) in response to this Office Action. Corrections will not be held in abeyance. Failure to submit a proper substitute specification in response to this Office Action will result in ABANDONMENT of the application.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-12, 18-21, 44-55 and 60-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-6, 18-21, 44-46, 48-50, 52-54 and 60-62 recite either the phrase "wherein it comprises" or "wherein it also comprises". This phrase renders the claims indefinite because it "it" is unclear and it is not definite what "it" is intended to refer to. Appropriate correction is required.

Regarding claim 1, the phrase "this sequence" renders the claim indefinite because it is unclear what "this sequence" refers to. Amending the claim to recite "said sequence" would obviate this rejection.

Regarding claims 1, 19 and 20, the phrase "in particular" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claims 1 and 10, the phrase "preferably" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 19 and 20 recite the phrase "gene optimized by substitution, by a signal sequence." This phrase renders the claims indefinite because 1) it is unclear how a gene can be "optimized"; and 2) it is unclear how a gene can be ""optimized by substitution, by a signal sequence". Appropriate correction is required.

Similarly, claim 21 recites the phrase "an expression plasmid encoding the F antigen of BRSV optimized by the insertion of the signal sequence of the human tPA". It is unclear if the

how insertion of "the human tPA" can optimize an expression plasmid encoding the F antigen of BRSV. Appropriate correction is required.

Claim 63 recites the limitation "the expression vector". There is insufficient antecedent basis for this limitation in the claim.

Claims 2-12, 18-21, 44-55 and 60-63 are dependent claims which encompass all of the embodiments of the claims from which they depend. Therefore, claims 2-12, 18-21, 44-55 and 60-63 are rejected for being indefinite the reasons above.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xiang et al. (Immunity 1995, 2:129-135) in view of Harris et al. (US Patent 5,719,131; 1998).

Xiang teaches a DNA vaccine against a pathogen affecting farm animals (here, mice), comprising a plasmid containing a nucleotide sequence encoding an immunogen of a pathogen of the animal species considered (here, the glycoprotein of rabies virus) under conditions allowing the in vivo expression of said nucleotide sequence (see p. 129, abstract and second column; p. 130, Figure 1 and Table 1); wherein the vaccine additionally comprises a plasmid expressing mouse GM-CSF (see p. 130, first paragraph; and p. 132 under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies virus").

Xiang does not teach that the vaccine comprises a cationic lipid containing a quaternary ammonium salt (such as DMRIE).

Harris teaches a cationic amphiphile comprised of DMRIE and DOPE which can be complexed to therapeutic molecules and used to facilitate the transport of the therapeutic molecules (such as plasmid DNA) into target cells in a subject (see abstract; and column 40, lines 45-52). Harris teaches "the complex structure, behavior and environment presented by an intact tissue that is targeted for intracellular delivery of biologically active molecules often interfere substantially with such delivery..." Administration of the amphiphile facilitates the transport of the therapeutic molecules into cells.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings Xiang and Harris to make a DNA rabies vaccine comprising a plasmid expressing an immunogen (taught by Xiang) and a plasmid expressing mouse GM-CSF (taught by Xiang), wherein the plasmids are complexed with DMRIE and

DOPE (taught by Harris), and wherein the genes are expressed in vivo, with a reasonable expectation of success. The motivation to create such a vaccine would have been to increase the efficacy of the DNA vaccine, by complexing DMRIE:DOPE to the therapeutic plasmids in order to facilitate the delivery of the plasmids into the cells (taught by Harris), and thus enhancing the immune response.

11. Claims 1-8, 18 and 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al. (Journ. General Virology 1997, 78:3195-3206) in view of Harris et al. (US Patent 5,719,131; 1998), Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733; 1992).

Taylor teaches a DNA vaccine against a pathogen (BRSV) affecting a farm animal (bovine) comprising a nucleic acid encoding an immunogen of a pathogen of the animal species considered (here, the F and G proteins of BRSV), under conditions allowing the in vivo expression of this sequence (see p. 3195, abstract; p. 3199, Figure 2; and p. 3200, under "Effect of vaccination on BRSV infection").

Taylor does not teach that: 1) the nucleic acid encoding the immunogen is a plasmid; 2) the vaccine comprises a cationic lipid containing a quaternary ammonium salt (such as DMRIE or DOPE); 3) the vaccine comprises a GM-CSF protein of the animal species considered or a plasmid encoding said GM-CSF protein.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid expressing an immunogen of a pathogen (here, a plasmid expressing the glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF protein of the animal

species considered (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 25).

Harris teaches a cationic amphiphile comprised of DMRIE and DOPE can be complexed to therapeutic molecules and used to facilitate the transport of the therapeutic molecules (such as plasmid DNA) into target cells in a subject (see abstract; and column 40, lines 45-52). Harris teaches "the complex structure, behavior and environment presented by an intact tissue that is targeted for intracellular delivery of biologically active molecules often interfere substantially with such delivery..." Administration of the amphiphile facilitates the transport of the therapeutic molecules into cells.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings Taylor, Harris, Xiang, and Baker to make a BRSV vaccine comprising a plasmid expressing an immunogen of BRSV and a plasmid expressing bovine GM-CSF wherein the plasmids are complexed with DMRIE and DOPE and wherein the genes are expressed in vivo, with a reasonable expectation of success. The motivation to create such a vaccine would have been to increase the efficacy of the BRSV vaccine taught by Taylor by making modifications that were known in the art and taught by Harris (as mentioned above), such as complexing DMRIE:DOPE to plasmids (see Harris) expressing BRSV immunogen(s)

(see Taylor) and GM-CSF (see Xiang) in order to facilitate the delivery of the plasmids into cells and to enhance the host's immune response. It would have been obvious to add a GM-CSF to the vaccine because Xiang teaches that GM-CSF enhances the immune response to DNA vaccines. Furthermore, it would have been obvious to substitute the mouse GM-CSF (taught by Xiang) with bovine GM-CSF (taught by Baker) because Taylor teaches that the vaccine is intended for bovines and bovine GM-CSF was known (see Baker).

12. Claims 1-9, 11, 12, 18-20, 44-47, 52-55 and 60 –63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al. (Journ. General Virology 1997, 78:3195-3206) in view of Harris et al. (US Patent 5,719,131; 1998), Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733; 1992) and further in view of Li et al. (WO 96/40945; 1996).

Taylor teaches a DNA vaccine against a pathogen (BRSV) affecting a farm animal (bovine) comprising a nucleic acid encoding an immunogen of a pathogen of the animal species considered (here, the F and G proteins of BRSV), under conditions allowing the in vivo expression of this sequence (see p. 3195, abstract; p. 3199, Figure 2; and p. 3200, under "Effect of vaccination on BRSV infection").

Taylor does not teach that: 1) the nucleic acid encoding the immunogen is a plasmid; 2) the vaccine comprises a cationic lipid containing a quaternary ammonium salt (such as DMRIE or DOPE); 3) the vaccine comprises a GM-CSF protein of the animal species considered or a plasmid encoding said GM-CSF protein; 4) the nucleic acid encoding the immunogen comprises a deletion of the transmembrane domain of the immunogen (F or G proteins); 5) the plasmid

containing the nucleic acid encoding the immunogen (F or G proteins) contains intron II of the rabbit beta-globin gene (a stabilizing intron).

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid expressing an immunogen of a pathogen (here, a plasmid expressing the glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF protein of the animal species considered (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 25).

Harris teaches a cationic amphiphile comprised of DMRIE and DOPE can be complexed to therapeutic molecules and used to facilitate the transport of the therapeutic molecules (such as plasmid DNA) into target cells in a subject (see abstract; and column 40, lines 45-52). Harris teaches "the complex structure, behavior and environment presented by an intact tissue that is targeted for intracellular delivery of biologically active molecules often interfere substantially with such delivery..." Administration of the amphiphile facilitates the transport of the therapeutic molecules into cells.

Li (WO 96/40945) teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in

a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings Taylor, Harris, Xiang, and Baker with Li to make a BRSV vaccine comprising a plasmid expressing an immunogen (the F or G protein of BRSV, as taught by Taylor) and a plasmid expressing bovine GM-CSF wherein the plasmids are complexed with DMRIE and DOPE and wherein the genes are expressed in vivo, and wherein the immunogen (F protein of G protein of BRSV) has the transmembrane region deleted, with a reasonable expectation of success. The motivation to create such a vaccine would have been to increase the efficacy of the BRSV vaccine taught by Taylor by making modifications that were known in the art, (such complexing DMRIE:DOPE to plasmids expressing BRSV immunogens and GM-CSF in order to facilitate the delivery of the plasmids and to enhance the host's immune response, as mentioned above. It also would have been obvious to substitute the mouse GM-CSF (taught by Xiang) with bovine GM-CSF (taught by Baker) because the vaccine is intended for bovines and bovine GM-CSF was known (see Baker).

Furthermore, it would have been obvious to make a modification in the plasmid expressing the immunogen (F protein or G protein as taught by Taylor) such that the plasmid

comprises a deletion of the transmembrane region of the immunogen, and an intron II of the rabbit beta-globin gene in order to stabilize the mRNA in order enhance efficacy of the vaccine, as taught by Li.

13. Claims 1-8, 10, 18-20, 48-51 and 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al. (Journ. General Virology 1997, 78:3195-3206) in view of Harris et al. (US Patent 5,719,131; 1998), Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733; 1992) and further in view of Choi et al. (Virology 1998, 250:230-240).

Taylor teaches a DNA vaccine against a pathogen (BRSV) affecting a farm animal (bovine) comprising a nucleic acid encoding an immunogen of a pathogen of the animal species considered (here, the F and G proteins of BRSV), under conditions allowing the in vivo expression of this sequence (see p. 3195, abstract; p. 3199, Figure 2; and p. 3200, under "Effect of vaccination on BRSV infection").

Taylor does not teach that: 1) the nucleic acid encoding the immunogen is a plasmid; 2) the vaccine comprises a cationic lipid containing a quaternary ammonium salt (such as DMRIE or DOPE); 3) the vaccine comprises a GM-CSF protein of the animal species considered or a plasmid encoding said GM-CSF protein; 4) the nucleic acid encoding the immunogen comprises a deletion of the transmembrane domain of the immunogen; 5) the plasmid encoding the immunogen also contains a nucleotide sequence encoding the human tissue plasminogen activator (tPA) signal sequence.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid expressing an immunogen of a pathogen (here, a plasmid expressing the

glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF protein of the animal species considered (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 25).

Harris teaches a cationic amphiphile comprised of DMRIE and DOPE can be complexed to therapeutic molecules and used to facilitate the transport of the therapeutic molecules (such as plasmid DNA) into target cells in a subject (see abstract; and column 40, lines 45-52). Harris teaches "the complex structure, behavior and environment presented by an intact tissue that is targeted for intracellular delivery of biologically active molecules often interfere substantially with such delivery..." Administration of the amphiphile facilitates the transport of the therapeutic molecules into cells.

Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings Taylor, Harris, Xiang, and Baker with Li to make a BRSV vaccine comprising a plasmid expressing the F protein of BRSV (taught by Taylor) and a plasmid expressing bovine GM-CSF wherein the plasmids are complexed with DMRIE and DOPE and wherein the genes are expressed in vivo, and wherein the F protein has the transmembrane deleted, with a reasonable expectation of success. The motivation to create such a vaccine would have been to increase the efficacy of the BRSV vaccine taught by Taylor by making modifications that were known in the art, (such complexing DMRIE:DOPE to plasmids expressing BRSV immunogens and GM-CSF in order to facilitate the delivery of the plasmids and to enhance the host's immune response, as mentioned above). It also would have been obvious to substitute the mouse GM-CSF (taught by Xiang) with bovine GM-CSF (taught by Baker) because the vaccine is intended for bovines.

Furthermore, it would have been obvious to make a modification in the plasmid expressing the immunogen (F protein of G protein as taught by Taylor) such that the plasmid comprises the human tPA signal sequence (as taught by Choi). Choi provides the motivation to include the human tPA signal sequence by indicating that addition of the human tPA sequence enhances expression of the immunogen/tPA fusion protein, and results in the an increased immune response (see p. 233, Table 2, where the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

14. Claims 1-12, 18-21, 44-55, and 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al. (Journ. General Virology 1997, 78:3195-3206) in view of Harris et al. (US Patent 5,719,131; 1998), Xiang et al. (Immunity 1995, 2:129-135), and Baker et al.

(US Patent 5,106,733; 1992) and further in view of Li et al. (WO 96/40945; 1996), Choi et al. (Virology 1998, 250:230-240), and Klein et al. (WO 98/02179, 1998).

Taylor teaches a DNA vaccine against a pathogen (BRSV) affecting a farm animal (bovine) comprising a nucleic acid encoding an immunogen of a pathogen of the animal species considered (here, the F and G proteins of BRSV), under conditions allowing the in vivo expression of this sequence (see p. 3195, abstract; p. 3199, Figure 2; and p. 3200, under "Effect of vaccination on BRSV infection").

Taylor does not teach that: 1) the nucleic acid encoding the immunogen is a plasmid; 2) the vaccine comprises a cationic lipid containing a quaternary ammonium salt (such as DMRIE or DOPE); 3) the vaccine comprises a GM-CSF protein of the animal species considered or a plasmid encoding said GM-CSF protein; 4) the nucleic acid encoding the immunogen comprises a deletion of the transmembrane domain of the immunogen (F or G proteins); 5) the plasmid containing the nucleic acid encoding the immunogen (F or G proteins) contains intron II of the rabbit beta-globin gene (a stabilizing intron); 6) the plasmid encoding the immunogen also contains a nucleotide sequence encoding the human tissue plasminogen activator (tPA) signal sequence; and 7) the vaccine comprises a plasmid encoding the F protein of BRSV (with the modifications above) and a second plasmid encoding the G protein of BRSV (with the modifications above).

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid expressing an immunogen of a pathogen (here, a plasmid expressing the glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF protein of the animal species considered (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132,

under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 25).

Harris teaches a cationic amphiphile comprised of DMRIE and DOPE can be complexed to therapeutic molecules and used to facilitate the transport of the therapeutic molecules (such as plasmid DNA) into target cells in a subject (see abstract; and column 40, lines 45-52). Harris teaches "the complex structure, behavior and environment presented by an intact tissue that is targeted for intracellular delivery of biologically active molecules often interfere substantially with such delivery..." Administration of the amphiphile facilitates the transport of the therapeutic molecules into cells.

Li (WO 96/40945) teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-

9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Klein teaches a two-step immunization procedure against the pyramyxoviridae family of viruses (which includes RSV) wherein the subject is administered a vector expressing either the F or G protein of RSV and subsequently administering at the F protein or G protein of RSV (see p. 8 through p.10).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings Taylor, Harris, Xiang, and Baker with Li to make a BRSV vaccine comprising a plasmid expressing an immunogen (the F or G protein of BRSV, as taught by Taylor) and a plasmid expressing bovine GM-CSF wherein the plasmids are complexed with DMRIE and DOPE and wherein the genes are expressed in vivo, and wherein the immunogen (F protein of G protein of BRSV) has the transmembrane region deleted, with a reasonable expectation of success. The motivation to create such a vaccine would have been to increase the efficacy of the BRSV vaccine taught by Taylor by making modifications that were known in the art, (such complexing DMRIE:DOPE to plasmids expressing BRSV immunogens and GM-CSF in order to facilitate the delivery of the plasmids and to enhance the host's immune response, as mentioned above. It also would have been obvious to substitute the mouse GM-CSF

(taught by Xiang) with bovine GM-CSF (taught by Baker) because the vaccine is intended for bovines.

Furthermore, it would have been obvious to make a modification in the plasmid expressing the immunogen (F protein or G protein as taught by Taylor) such that the plasmid comprises a deletion of the transmembrane region of the immunogen, and an intron II of the rabbit beta-globin gene in order to stabilize the mRNA in order enhance efficacy of the vaccine, as taught by Li; and to make a modification in the plasmid expressing the immunogen (F protein of G protein as taught by Taylor) such that the plasmid comprises the human tPA signal sequence (as taught by Choi), as mentioned above.

Additionally, it would have been obvious to make A BRSV vaccine comprises a plasmid encoding the F protein of BRSV (with the modifications above) and a second plasmid encoding the G protein of BRSV (with the modifications above) wherein the vaccine comprises administration of a plasmid expressing the F protein of BRSV and the G protein of BRSV. The motivation to do so is provided by Klein. Klein teaches, "this [two-step] strategy leads to a stronger protective immune response than other strategies and to the production of a more balanced Th1/Th2 type response than previously attained" thus indicating that administration of two immunogens (here, BRSV-F and BRAV-G) would enhance the immune response to the vaccine.

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
September 5, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER